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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/697,613	10/26/2000	Harold A. Chapman	18989-006 (BWH-6)	4800

30623 7590 10/01/2002

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EXAMINER

SRIVASTAVA, KAILASH C

ART UNIT	PAPER NUMBER
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1651

DATE MAILED: 10/01/2002

8

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/697,613

Applicant(s)

CHAPMAN ET AL.

Examiner

DR. Kailash C. Srivastava

Art Unit

1651

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 06/13/2002(Paper Number 7) .
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1 and 5-14 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1 and 5-14 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4 . 6) ☐ Other: _____

DETAILED ACTION

1. Applicants' preliminary amendment filed 06/13/2002 (Paper Number 7) is acknowledged and entered.
2. Claims 2-4 and 15-21 have been cancelled
3. Claims 1, 5 and 11-14 have been amended.
4. Claims 1 and 5-14 are pending.
5. Applicant's response filed 06/13/2002 (Paper Number 7) to election requirement in Office Action dated 12/13/2001 (paper Number 5) is acknowledged and entered.

Restriction/Election

6. Applicants' election without traverse of Group I, Claims 1 and 5-14 is acknowledged and entered. Applicants' election of species to atherosclerosis as the vascular disease, Cystatin C as the protease inhibitor and Cathepsin S as the cysteine protease is also acknowledged.
7. Claims 1 and 5-14 are examined on merits.

Objection to Information Disclosure Statement

8. The information disclosure statement (i.e., IDS) filed 08/02/2001 (Paper Number 4) is deficient. In its present form, the IDS does not furnish titles of the cited references C1-C65 and cites volume numbers of the cited publications just after the author's name. The volume number for the reference should be cited after the name of the publication. Applicants are requested to resubmit the IDS with appropriate correction to the IDS as outlined above.

Claim Rejections - 35 U.S.C. § 112

9. The following is a quotation of the second paragraph of 35 U.S.C. § 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.
10. Claim 1 is rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- While applicant may be his or her own lexicographer, a term in a claim may not be given a meaning repugnant to the usual meaning of that term. See *In re Hill*, 161 F.2d 367, 73 USPQ 482 (CCPA 1947). The term "athersclerosis" in claim 1 is used to mean "arteriosclerosis". Appropriate correction should be made.

Claim Rejections – 35 U.S.C. § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims ⁵⁻1-8 are rejected under 35 U.S.C. §102(b) as anticipated by Grubb et al (U.S. Patent 5,037,957).

Claims recite a method to treat atherosclerosis in a subject by administering to the said subject a composition comprising an inhibitor of a cysteine protease, wherein the said protease consists of cathepsin S, and the said protease inhibitor comprises a cystatin. Furthermore, the said protease inhibitor comprises a cystatin C polypeptide wherein the said polypeptide comprises a cystatin C active site.

Grubb et al., disclose a method wherein cysteine proteinase inhibitor cystatin C is administered as a pharmaceutical preparation for prophylactic treatment of conditions where inhibition of cysteine proteinase is desired (Column 3, Lines 5-10 and 40-44). Such conditions are ischemic injuries (e.g., infarction), wherein cardiac body tissues are damaged because of the activity of cystein proteinases (Column 1, Lines 15-18 and 28-36). The said cystatin C is constituted of polypeptide chain (Column 3, Line 15) and comprises a cystatin C active site (Column 3, Lines 16-25). Furthermore, since Grubb et al., have tested the activity of their cystatin C containing protease inhibitor with papain (Column 8, Lines 35-45), the cystein protease inhibitor that Grubb et al., have tested inherently contains cathepsin S because Cathepsin S constitutes papain family of enzymes.

Therefore, the reference is deemed to anticipate the cited claims.

13. Claims 13-14 are rejected under 35 U.S.C. §102(b) as anticipated by Iwata et al (U.S. Patent 5,262, 319).

Claims recite a method to treat or prevent atherosclerosis in a subject by administering to the said subject transforming growth factor beta.

Iwata et al., disclose treating a subject suffering from atherosclerosis by administering TGF- β to the said subject (Column 8, Lines 18-22).

Therefore, the reference is deemed to anticipate the cited claims.

Claim Rejections - 35 U.S.C. § 103

14. The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

15. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103(a).

16. Claims 1-14 are rejected under 35 U.S.C. § 103 (a) as obvious over Grubb et al (U.S. Patent 5,037,957), in view of Emmanuel et al (U.S. Patent 6,420,364) and Iwata et al (U.S. Patent 5,262, 319).

Claims recite a method to treat or prevent atherosclerosis in a subject by administering to the said subject a composition comprising an inhibitor of a cysteine protease, wherein the said protease consists of cathepsin S, and the said protease inhibitor comprises a cystatin. Furthermore, the said protease inhibitor comprises a cystatin C polypeptide wherein the said polypeptide comprises a cystatin C active site. The said composition is administered locally at the site of vascular injury or systemically. The claims further recite a method to treat or prevent atherosclerosis in a subject by administering to the said subject transforming growth factor beta.

As discussed in item 12 *supra*, Grubb et al., disclose a method wherein cysteine proteinase inhibitor cystatin C is administered as a pharmaceutical preparation for prophylactic treatment of conditions where inhibition of cysteine proteinase is desired (Column 3, Lines 5-10 and 40-44). Such conditions are ischemic injuries (e.g., infarction), wherein cardiac body tissues are damaged because of the activity of cystein proteinases (Column 1, Lines 15-18 and 28-36). The said cystatin C is constituted of polypeptide chain (Column 3, Line 15) and comprises a cystatin C active site (Column 3, Lines 16-25). Since Grubb et al., have tested the activity of their cystatin C containing protease inhibitor with papain (Column 8, Lines 35-45), the cystein protease that Grubb et al., have tested intrinsically contains cathepsin S. Grubb et al., disclose prophylactic treatment of atherosclerosis by administering cystatin C containing proteinase inhibitor. Therefore, they disclose prevention as well as treatment of atherosclerosis in a subject.

Grubb et al., however, have not clearly disclosed that their cysteine protease consists of Cathepsin S. Emmanuel et al., disclose that cathepsin S and other cathepsin are members of the papain family within the superfamily of cysteine proteases. Emmanuel et al., further disclose that papain family of proteases plays an important role in human disease, e.g., atherosclerosis, among others (Column 1, Lines 21-30). Thus, Emmanuel et al., clearly disclose that cathepsin S has a clear role in atherosclerosis. Emmanuel et al., further disclose treating atherosclerosis by administering one of the compounds disclosed in the said patent (Column 193, Lines 25-28).

None of the above cited references, however, disclose treating or preventing atherosclerosis by administering transforming growth factor β (i.e., TGF- β).

As discussed in item 13 *supra*, Iwata et al., disclose treating a subject suffering from atherosclerosis by administering TGF- β to the said subject (Column 8, Lines 18-22).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify Grubb et al method of treating atherosclerosis by clarifying that their cysteine protease contains cathepsin S and further modifying their composition by incorporating TGF- β in their composition according to the beneficial teachings from Iwata et al., because each one of the cited prior art references teach a method to treat atherosclerosis, prophylactic or non-prophylactic by administering either a protease inhibitor (Column 3, Lines 5-10 and 40-44; Column 1, Lines 15-18 and 28-36; Column 3, Line 15; Column 3, Lines 16-25; Column 8, Lines 35-45) or TGF- β (Column 8, Lines 18-22).

One having ordinary skill in the art would have been motivated to modify Grubb et al's composition according to the beneficial teachings from Iwata et al., because both prior art references teach treating atherosclerosis.

None of the prior art references cited above teach the mode of application or administering their compositions to prophylactically or non-prophylactically treat atherosclerosis. However, the adjustment of particular conventional working conditions (e.g., systemic, local or topical application of a pharmaceutical composition) is deemed merely a matter of judicious selection and routine optimization which is well within the purview of the skilled artisan.

From the teachings of the cited references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.


CONCLUSION

17. No Claims are allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Kailash C. Srivastava whose telephone number is (703) 605-1196. The examiner can normally be reached on Monday-Thursday from 7:30 A.M. to 6:00 P. M. (Eastern Standard Time or Eastern Daylight Saving Time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn, can be reached on (703) 308-4743 Monday through Thursday. The fax phone number for the organization where this application or proceeding is assigned is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.


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Art Unit 1651
(703) 605-1196

September 27, 2002



CHRISTOPHER R. TATE
PRIMARY EXAMINER